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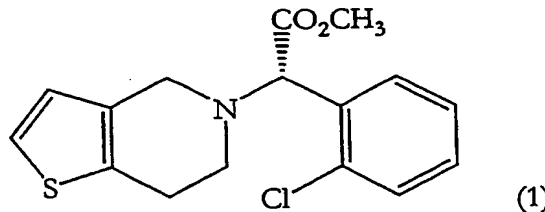
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(54) Title: NOVEL CRYSTALLINE POLYMORPHS OF CLOPIDOGREL



(57) Abstract: The present invention relates to novel crystalline forms of the platelet aggregation inhibitor (+)-(S)-methyl-2-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate, clopidogrel (1), in the form of hydrogen bromide salts, identified as polymorph forms 1, 2 and 3. The present invention further relates to processes for preparing such forms, pharmaceutical compositions comprising such forms, and uses for such forms and compositions. The pharmaceutical compositions may be used, in particular, for inhibiting platelet aggregation or for treating, preventing or managing thrombosis, atherothrombosis, an atherothrombotic event, ischaemic stroke, myocardial infarction, non-Q-wave myocardial infarction, atherosclerosis, peripheral arterial disease, or unstable angina. The present invention also relates to methods of treating said disorders. Formula (1).

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Novel Crystalline Compounds

Background art

The present invention relates to novel crystalline forms of the platelet aggregation
5 inhibitor (+)-(S)-methyl-2-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-
yl)acetate, clopidogrel (1), in the form of hydrogen bromide salts. The present
invention further relates to processes for preparing such forms, pharmaceutical
compositions comprising such forms, and uses for such forms and compositions.

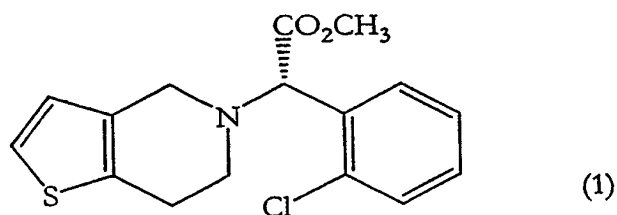
10 The pharmaceutical compositions may be used, in particular, for inhibiting platelet
aggregation or for treating, preventing or managing thrombosis, atherothrombosis,
an atherothrombotic event, ischaemic stroke, myocardial infarction, non-Q-wave
myocardial infarction, atherosclerosis, peripheral arterial disease, or unstable angina.
The present invention also relates to methods of treating said disorders.

15

Technical field

The manufacturing process for many pharmaceuticals is hindered by the fact that
the organic compound, which is the active drug substance, has handling difficulties
during the manufacturing process and undesirable properties being imparted to the
20 final drug or dosage form. In addition it can be difficult to control the polymorphic
form of the active drug substance throughout the manufacturing process.

Previous preparations of clopidogrel (1) are reported in patent applications EP 0
420 706, EP 0 099 802, WO 98/51689, WO 98/51682, WO 98/51681, EP 0 466 569
25 and EP 0 281 459.



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Clopidogrel is currently marketed as the hydrogen sulfate salt and polymorphic forms of this hydrogen sulfate salt have been reported in WO 99/65915. However, to date there have been no reports of polymorphs of the hydrogen bromide salt of clopidogrel.

5

Summary of the invention

It is an object of the present invention to provide clopidogrel in a solid crystalline form that affords the compound improved handling properties and/or improved properties as a pharmaceutical agent and enables control of the polymorphic form during manufacturing.

10

Accordingly, a first aspect of the present invention provides clopidogrel hydrogen bromide in polymorph form 1 (hydrate). Preferably the clopidogrel hydrogen bromide in polymorph form 1 has a DSC trace substantially as shown in Figure One, an XRPD spectrum substantially as shown in Figure Four, and/or TGA data substantially as shown in Figure Seven.

15

A second aspect of the present invention provides clopidogrel hydrogen bromide in polymorph form 2 (anhydrate). Preferably the clopidogrel hydrogen bromide in polymorph form 2 has a DSC trace substantially as shown in Figure Two, an XRPD spectrum substantially as shown in Figure Five, and/or TGA data substantially as shown in Figure Eight.

20

A third aspect of the present invention provides clopidogrel hydrogen bromide in polymorph form 3 (anhydrate). Preferably the clopidogrel hydrogen bromide in polymorph form 3 has a DSC trace substantially as shown in Figure Three, an XRPD spectrum substantially as shown in Figure Six, and/or TGA data substantially as shown in Figure Nine.

25

Preferably the clopidogrel hydrogen bromide in polymorph form 1, 2 or 3 is in particulate form. Preferably the clopidogrel hydrogen bromide in polymorph form 1, 2 or 3 is substantially pure.

30

In the context of the present application, the term "substantially pure" clopidogrel hydrogen bromide in polymorph form 1 means that the clopidogrel hydrogen bromide in polymorph form 1 comprises less than 20% of other crystalline or amorphous forms of clopidogrel hydrogen bromide, preferably less than 15%, more preferably less than 10%, more preferably less than 5%, more preferably less than 2%, more preferably less than 1%, and even more preferably less than 0.5%. The term "substantially pure" also means that the clopidogrel hydrogen bromide in polymorph form 1 comprises less than 3% of other impurities, preferably less than 2%, more preferably less than 1%, and even more preferably less than 0.5%. The term "substantially pure" is defined accordingly in the context of clopidogrel hydrogen bromide in polymorph form 2 or polymorph form 3.

Preferably the clopidogrel hydrogen bromide in polymorph form 1, 2 or 3 is for use as a medicament. Preferably the medicament is for inhibiting platelet aggregation or for treating, preventing or managing thrombosis, atherothrombosis, an atherothrombotic event, ischaemic stroke, myocardial infarction, non-Q-wave myocardial infarction, atherosclerosis, peripheral arterial disease, or unstable angina.

Fourth, fifth and sixth aspects of the invention provide processes for the respective preparation of the clopidogrel hydrogen bromide of the first, second and third aspects of the invention.

The compounds of the invention are preferably preparable or prepared by a process comprising crystallisation from a solution in an organic solvent or solvents. Said process, in an embodiment, also comprises the step of drying the precipitate to provide a crystalline form in accordance with the first, second or third aspect of the invention. The compound can be dried under conventional vacuum drying conditions, for example, under a vacuum of down to 50, 40, 35, 30, 25 or 20 mmHg, preferably 30 mmHg, and at a temperature of up to 20, 25, 30, 35, 40, 45, 50, 55 or 60°C, preferably 45°C. Preferably the organic solvent is polar, miscible with water, dipolar, and/or aprotic. Optionally the organic solvent comprises a plurality or mixture of solvent compounds. The organic solvent may be 2-propanol, diisopropyl ether, *t*-butylmethyl ether, dichloromethane, methanol, and/or ethanol.

Clopidogrel hydrogen bromide in polymorph form 1 is preferably prepared by recrystallisation from a mixture of 2-propanol and diisopropyl ether, preferably in a 2-propanol: diisopropyl ether ratio of from 50:50 to 70:30, preferably about 60:40.
5 Preferably the recrystallisation is carried out at 20-35°C for 1-6 hours followed by 0-15°C for 0.1-4 hours; more preferably the recrystallisation is carried out at 25-30°C for 1.5-3 hours followed by 5-10°C for 0.5-1.5 hours.

Clopidogrel hydrogen bromide in polymorph form 2 is preferably prepared by
10 recrystallisation from a mixture of 2-propanol and diisopropyl ether, preferably in a 2-propanol: diisopropyl ether ratio of from 1:10 to 40:60, preferably from 10:90 to 30:70. Preferably the recrystallisation is carried out at 20-35°C for 1-6 hours; more preferably the recrystallisation is carried out at 25-30°C for 1.5-3 hours.

15 Alternatively, clopidogrel hydrogen bromide in polymorph form 2 may be prepared by recrystallisation from *t*-butylmethyl ether. Preferably the recrystallisation is carried out at 20-35°C for 0.5-4 hours; more preferably the recrystallisation is carried out at 27-32°C for 0.5-2 hours.

20 Clopidogrel hydrogen bromide in polymorph form 3 is preferably prepared by recrystallisation from a mixture of methanol or ethanol with water, preferably in an alcohol: water ratio of from 5:95 to 20:80, preferably about 10:90. Preferably the recrystallisation is carried out at 2-10°C for 8-20 hours; more preferably the recrystallisation is carried out at 3-8°C for 10-15 hours.

25 Compounds in accordance with the first, second and third aspects of the invention can be used to advantage in the preparation of pharmaceutical dosage or drug forms. Accordingly, in further aspects, the present invention provides a method of preparing a pharmaceutical dosage form that utilises compounds in accordance with
30 the first, second and third aspects of the invention.

The present invention also provides a pharmaceutical composition prepared or preparable by such a method. The pharmaceutical composition of the present

invention may be for immediate, sustained or delayed release. The composition is preferably solid and comprises a compound in accordance with the first, second or third aspect of the invention, in addition to one or more conventional pharmaceutically acceptable carrier(s), excipient(s) or diluent(s). Preferred
5 pharmaceutical compositions in accordance with the invention include tablets, capsules and the like.

The pharmaceutical composition of the present invention can be administered by oral, parental (including intravenous, subcutaneous, intramuscular, intradermal,
10 intratracheal, intraperitoneal, intraarticular, intracranial and epidural), transdermal, airway (aerosol), rectal, vaginal or topical (including buccal, mucosal and sublingual) administration. Preferably the composition is for oral administration.

For oral administration, the pharmaceutical composition of the invention will
15 generally be provided in the form of tablets, capsules, hard or soft gelatine capsules, caplets, troches or lozenges, as a powder or granules, or as an aqueous solution, suspension or dispersion. Solutions, suspensions and dispersions may be prepared from powder or granules of clopidogrel hydrogen bromide in polymorph form 1, 2 or 3. Preferably the composition is in the form of tablets or capsules.

20

Tablets for oral use may include clopidogrel hydrogen bromide in polymorph form 1, 2 or 3 mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable excipients are
25 mannitol, macrogol, microcrystalline cellulose, hydrogenated castor oil, and low substituted hydroxypropylcellulose. Tablets can be prepared by conventional techniques, including direct compression, wet granulation and dry granulation. If desired, the tablets may be coated with materials such as hypromellose, lactose, triacetin, and/or carnauba wax.

30

Capsules for oral use include hard gelatine capsules in which clopidogrel hydrogen bromide in polymorph form 1, 2 or 3 is mixed with a solid diluent, and soft gelatine

capsules wherein clopidogrel hydrogen bromide in polymorph form 1, 2 or 3 is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

Formulations for rectal administration may be presented as a suppository with a
5 suitable base comprising, for example, cocoa butter or a salicylate.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

10

For parenteral use, the compounds of the present invention will generally be provided in a sterile aqueous solution or suspension, buffered to an appropriate pH and isotonicity. Such solutions and suspensions may be prepared from powder or granules of clopidogrel hydrogen bromide in polymorph form 1, 2 or 3. Suitable
15 aqueous vehicles include Ringer's solution and isotonic sodium chloride or glucose. Aqueous suspensions according to the invention may include suspending agents such as cellulose derivatives, sodium alginate, polyvinylpyrrolidone and gum tragacanth, and a wetting agent such as lecithin. Suitable preservatives for aqueous suspensions include ethyl and n-propyl p-hydroxybenzoate. The compounds of the
20 invention may also be presented as liposome formulations.

For topical and transdermal administration, the compounds of the invention will generally be provided in the form of ointments, cataplasms (poultices), pastes, powders, dressings, creams, plasters or patches.

25

Suitable suspensions and solutions can be used in inhalers for airway (aerosol) administration. Such suspensions and solutions may be prepared from powder or granules of clopidogrel hydrogen bromide in polymorph form 1, 2 or 3.

30 Preferably the pharmaceutical composition is in unit dosage form comprising clopidogrel hydrogen bromide in polymorph form 1, 2 or 3 in an amount of from 1mg to 300mg with respect to the free base, preferably in an amount of from 5mg

to 200mg, more preferably in an amount of from 10mg to 125mg, and more preferably in an amount of from 50mg to 100mg.

The clopidogrel hydrogen bromide of the present invention is effective over a wide
5 dosage range, the actual dose administered being dependent on the condition being treated. For example, in the treatment of adult humans, dosages from 1mg to 300mg, preferably from 10mg to 125mg, more preferably from 50mg to 100mg with respect to the free base per day may be used. The desired dose is normally presented once a day, but may be dosed as two, three, four or more sub-doses
10 administered at appropriate intervals throughout the day.

Preferably the pharmaceutical composition of the present invention is for inhibiting platelet aggregation or for treating, preventing or managing thrombosis, atherothrombosis, an atherothrombotic event, ischaemic stroke, myocardial
15 infarction, non-Q-wave myocardial infarction, atherosclerosis, peripheral arterial disease, or unstable angina.

In further aspects, the present invention provides a method of inhibiting platelet aggregation, comprising administering an effective amount of clopidogrel hydrogen
20 bromide in polymorph form 1, 2 or 3 to a patient in need thereof. The present invention also provides a method of treating, preventing or managing a condition selected from thrombosis, atherothrombosis, an atherothrombotic event, ischaemic stroke, myocardial infarction, non-Q-wave myocardial infarction, atherosclerosis, peripheral arterial disease, and unstable angina, comprising administering an
25 effective amount of clopidogrel hydrogen bromide in polymorph form 1, 2 or 3 to a patient in need thereof. Preferably the patient is a human. Preferably the amount of clopidogrel hydrogen bromide administered is from 10mg to 125mg, preferably from 50mg to 100mg with respect to the free base per day.

30 In a further aspect of the invention, there is provided the use of a compound in accordance with the first, second or third aspect of the invention for the manufacture of a medicament for the inhibition of platelet aggregation and consequently the treatment, prevention and/or management of such diseases as

thrombosis, atherothrombosis, an atherothrombotic event, ischaemic stroke, myocardial infarction, non-Q-wave myocardial infarction, atherosclerosis, peripheral arterial disease or unstable angina.

- 5 The compounds in accordance with the first, second and third aspects of the invention may also be useful as precursors to other novel or known polymorphic forms of clopidogrel that may be useful in the preparation of pharmaceutical products. Alternatively, the compounds in accordance with the first, second and third aspects of the invention may be used to prepare other desired polymorphic
- 10 forms of clopidogrel hydrogen sulfate in a more controllable manner. The present invention therefore provides a process for preparing a polymorphic form of clopidogrel hydrogen sulfate, comprising the step of using clopidogrel hydrogen bromide in polymorph form 1, 2 or 3.
- 15 The present invention is illustrated, but in no way limited, by the following examples and figures.

Brief description of the figures

Figure One is a DSC trace of polymorph form 1 clopidogrel hydrogen bromide.

- 20 Figure Two is a DSC trace of polymorph form 2 clopidogrel hydrogen bromide.

Figure Three is a DSC trace of polymorph form 3 clopidogrel hydrogen bromide.

Figure Four is an XRPD spectrum of polymorph form 1 clopidogrel hydrogen bromide.

- 25 Figure Five is an XRPD spectrum of polymorph form 2 clopidogrel hydrogen bromide.

Figure Six is an XRPD spectrum of polymorph form 3 clopidogrel hydrogen bromide.

Figure Seven shows TGA data for polymorph form 1 clopidogrel hydrogen bromide.

- 30 Figure Eight shows TGA data for polymorph form 2 clopidogrel hydrogen bromide.
- Figure Nine shows TGA data for polymorph form 3 clopidogrel hydrogen bromide.

Detailed description of the invention/Examples(±)-2-(2-Chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetonitrile

5 To a mixture of methanol (2.50l) and water (250ml) was charged 4,5,6,7-tetrahydro-thieno[3,2-c]pyridine hydrochloride (500g; 2.85mol) with stirring. After stirring for 10 minutes, sodium cyanide (153.0g; 3.12mol) was added and stirred further for 40 minutes. 2-Chlorobenzaldehyde (392.1g; 2.79mol) was added slowly to this reaction mixture between 23-28°C over a period of 1.5 hours. After the addition was over,
10 the flask was heated in an oil bath between 40-50°C and maintained at this temperature for 4.5 hours. After cooling the reaction mixture to 25-30°C, 5% sodium metabisulfite solution (250ml) was added and stirred for 1 hour at this temperature range. To the resulting slurry, water (7.5l) was added and stirred for 1 hour at 25-30°C. The off-white solid thus formed was filtered, washed with a 1:1
15 mixture of methanol: water (2.5l) and the wet cake was dried at 75°C under vacuum (pressure: -0.8kg/cm²) for 10 hours to obtain the product as an off-white solid. Yield: 719.0g (87.4%). mp: 124-126.5°C. The product was identified by IR spectrum, ¹H and ¹³C NMR investigation.

20 (±)-2-(2-Chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide

(±)-2-(2-Chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetonitrile (713g; 2.46mol) was added to methanol (3.505l) at 23-28°C with stirring. To this slurry, potassium carbonate (170g; 1.23mol) was added followed by dimethyl sulfoxide
25 (263ml; 3.7mol). The contents were heated between 30-40°C and 30.0% aqueous hydrogen peroxide solution (382ml; 3.70mol) was added between 40-50°C slowly over a period of 3 hours. After the addition was over, the reaction mixture was maintained at this temperature for a further 2 hours, after which the reaction was brought to 20-30°C. 35% Hydrochloric acid (213.0ml) in water (10.7l) was added
30 slowly to the reaction mixture over a period of 1 hour 15 minutes. After stirring for 1 hour, the solid formed was filtered and washed with a 1:1 methanol: water mixture (3.565l). The isolated solid was dried in a vacuum oven at 75-80°C for a period of

12 hours. Yield: 716g (94.72%). mp: 124-126°C. The product was identified by IR spectrum, ¹H and ¹³C NMR investigation.

(+)-(1S)-Camphor-10-sulfonic acid salt of (S)-2-(2-Chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide

(a) To a stirred slurry of (±)-2-(2-chlorophenyl)-6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide (710g; 2.315mol) in acetone (3.56l) and methanol (0.355l) maintained at 23-28°C was added a solution of (+)-(1S)-camphor-10-sulfonic acid (270g; 1.16mol) dissolved in acetone (1.44l) over a period of 1 hour. After stirring for another hour, formic acid (98-100%; 53.8g; 1.16mol) was added all at once and stirred for 1 hour, after which the reaction mixture was cooled to 0-10°C and kept at this temperature for another 1 hour 30 minutes. The solid thus formed was filtered and washed with acetone (1.44l) and dried in a vacuum oven between 60-65°C for a period of 6 hours. Yield: 470.0g (38% by theory, based on the enantiomer content). mp: 194-208°C. $[\alpha]_D^{25}$: +41.5 (c=1.0g/100ml; methanol).

(b) Isolation of (±)-2-(2-Chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide from the mother liquor obtained in step (a)

To the mother liquor obtained in step (a), 20% aqueous solution of sodium hydroxide (710ml) was added at 26-27°C with stirring. The reaction mixture was heated to 45-50°C and maintained at that temperature for 5 hours. The reaction mixture was concentrated to 1/10 of its volume under vacuum. The resulting slurry was cooled to 30°C and methanol (710ml) was added followed by water (4.9l) slowly to the reaction mixture over a period of 30 minutes. The pH of the reaction mass was adjusted to 7-7.5 by the addition of 15% hydrochloric acid solution (1.2l). After stirring for an hour, the solid formed was filtered and washed with water (3.5l). The isolated solid was dried in a vacuum oven (pressure: -0.8kg/cm²) between 75-80°C for a period of 14 hours. Yield: 393g. mp: 128-134°C.

(c) (±)-2-(2-Chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide obtained in step (b) was converted to (+)-(1S)-camphor-10-sulfonic acid salt of (S)-2-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide by following

the procedure mentioned in step (a). Yield: 240.0g (36% by theory, based on the enantiomer content). mp: 202-210°C. $[\alpha]_D^{25}$: +47.5 (c=1.0g/100ml; methanol).

(d) The (+)-(1S)-camphor-10-sulfonic acid salt of (S)-2-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide (700g; 1.298mol) obtained was charged into methanol (1.75l) with stirring at 23-28°C. The contents were heated to 60°C and the temperature was maintained at this temperature for 2 hours. To this clear solution, acetone (7.0l) was added and the temperature was maintained at this temperature for 1 hour. The reaction mixture was cooled between 0-5°C and stirred for another 1 hour and 30 minutes. The solid thus precipitated was filtered, washed with acetone (1.4l) and dried between 60-65°C under vacuum (-0.8kg/cm²) for 7 hours. Yield: 545.0g (77.85% by theory). mp: 210-218°C. $[\alpha]_D^{25}$: +51.69 (c=1.0g/100ml; methanol).

15 (+)-(S)-2-(2-Chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide

The crystallized (+)-(1S)-camphor-10-sulfonic acid salt of (S)-2-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetamide (521.0g; 0.966mol) was charged into methanol (2.605l) with stirring at 23-28°C followed by water (1.042l). To this clear solution, activated carbon (10.42g) was added and the contents were stirred for 1.5 hours at this temperature. The activated carbon was filtered off by passing the contents of the flask through a bed of celite on a Buchner funnel and the residue in the funnel was washed with a water: methanol mixture (3:7; 0.521l). To the combined filtrate, 2% (w/v) aqueous sodium bicarbonate solution (4.168l) was added over a period of 30 minutes and stirred for 1 hour and 30 minutes. The solid precipitated was filtered, washed with methanol: water (2.084l; 1:1 v/v) and dried under vacuum (-0.8kg/cm²) for a period of 8 hours between 70-75°C. Yield: 284.0g (95.8% by theory). mp: 154-156°C. $[\alpha]_D^{25}$: +39.5 (c=1.0g/100ml; methanol). The product was identified by IR spectrum, ¹H and ¹³C NMR investigation.

(+)-(S)-Methyl-2-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate
(clopidogrel)

Concentrated sulfuric acid (~98%; 496ml; 9.30mol) was charged into methanol
5 (1.75l) with stirring between 25-38°C followed by dimethyl sulfate (250ml;
2.636mol). The contents were heated to reflux for 3 hours, after which the reaction
mixture was cooled to 40-50°C and (+)-(S)-2-(2-chlorophenyl)-(6,7-dihydro-4H-
thieno[3,2-c]pyrid-5yl)acetamide (500g; 1.55mol) was charged. The reaction mixture
10 was heated to 65°C and maintained between 65-66°C for a period of 60 hours. The
reaction mixture was cooled to 25-30°C and poured into water (10.0l) with stirring.
Dichloromethane (5.0l) was added, stirred for 1 hour, after which the organic layer
was separated. To the aqueous layer dichloromethane (2.5l) was added and stirred
for 1 hour and the separated organic layer was combined with the earlier separated
layer and washed with water (2.5l). 5% (w/v) aqueous sodium bicarbonate solution
15 (2.5l) was added to this organic layer and stirred for a period of an hour and the
separated organic layer was washed with 0.25% sulfuric acid (2.5l) followed by water
(2.5l) and treated with activated carbon (40.0g) for a period of 3 hours with stirring.
The activated carbon was removed by filtration through a celite bed and the celite
bed was washed with dichloromethane (1.0l). This washing was coupled with the
20 filtrate and the solvent removed under vacuum to yield (+)-(S)-2-(2-chlorophenyl)-
(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetic acid methyl ester as a pale yellow oil.
Yield: 380g (73.0% by theory). The product was identified by IR spectrum, ¹H and
¹³C NMR investigation.

25 (+)-(S)-Methyl-2-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate
(clopidogrel) hydrogen bromide polymorph form 1

Method 1: To a stirred solution of (+)-(S)-methyl-2-(2-chlorophenyl)-(6,7-dihydro-
4H-thieno[3,2-c]pyrid-5-yl)acetate (20g; 0.062mol) in 2-propanol (60ml) and
30 diisopropyl ether (40ml) was added ~47% aqueous hydrobromic acid solution
(10.88g; 0.0631mol of HBr) with stirring between 20-26°C over a period of 20
minutes. The contents were stirred for 2 hours and 30 minutes between 26-28°C,
cooled to 10°C and maintained at this temperature for 30 minutes. The precipitated

solid was filtered, washed twice with diisopropyl ether (20ml each time) and dried in a vacuum oven between 45-50°C for 4 hours.

The product was characterised by DSC and XRPD (see Figures One and Four respectively). TGA indicated that the product is a hydrate form (see Figure Seven). There are two peaks in the DSC trace indicating the evaporation of water followed by a peak indicating the anhydrate form (polymorph form 3).

Method 2: (+)-(S)-Methyl-2-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate hydrogen bromide (69g) was charged into 2-propanol (760ml) with stirring at 25-26°C. The contents were heated between 45-50°C. To this clear solution, activated carbon (3.7g) was added and the reaction temperature was maintained at 38°C for 1 hour. The contents were cooled to 26-28°C. The activated carbon was filtered off by passing the contents of the flask through a bed of celite on a Buchner flask and the residue in the funnel was washed with 2-propanol (140ml). To the combined filtrate, diisopropyl ether (690ml) was added and stirred for 2 hours at 26-27°C. The reaction contents were cooled to 0-5°C and maintained at this temperature for 1 hour. The solid precipitated was filtered, washed twice with diisopropyl ether (140ml each time) and dried in a vacuum oven between 45-50°C for 5 hours. Yield: 57g (82.6%).

(+)-(S)-Methyl-2-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate (clopidogrel) hydrogen bromide polymorph form 2

Method 1: (+)-(S)-Methyl-2-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate hydrogen bromide (220g) was charged into 2-propanol (242ml) with stirring at 25-26°C. The contents were heated to 50°C. To this clear solution, activated carbon (4.4g) was added and the reaction temperature was maintained between 34-40°C for 1 hour. The contents were cooled to 26-28°C. The activated carbon was filtered off by passing the contents of the flask through a bed of celite on a Buchner flask and the residue in the funnel was washed with 2-propanol (440ml). To the combined filtrate, diisopropyl ether (2.2l) was added and stirred for 2 hours at 26-27°C. The solid precipitated was filtered, washed twice with

diisopropyl ether (440ml each time) and dried in a vacuum oven between 45-50°C for 5 hours. Yield: 147g (66%).

Method 2: To a stirred solution of (+)-(S)-methyl-2-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetic acid (22g; 0.068mol) in *t*-butylmethyl ether (110ml) was added hydrogen bromide in acetic acid solution (~33%; 12.69ml; 0.072mol of HBr) with stirring between 20-26°C over a period of 20 minutes. To the reaction mixture, 2-propanol (110ml) was added and the reaction mixture was heated to 40°C. The contents were cooled to 30°C and stirred for 45 minutes between 28-30°C. The precipitated solid was filtered, washed with *t*-butylmethyl ether: 2-propanol (1:1; 44ml) followed by *t*-butylmethyl ether (22ml each time) and dried in a vacuum oven (-0.8kg/cm²) between 45-50°C for 6 hours. Yield: 16g (58%).

Method 3: To a stirred solution of (+)-(S)-methyl-2-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetic acid (10g; 0.031mol) in dichloromethane (40ml) was added ~47% aqueous hydrobromic acid solution (3.56ml; 0.031mol of HBr) with stirring between 20-21°C over a period of 10 minutes. The contents were stirred for 3 hours between 26-27°C. The reaction mixture was dried over sodium sulfate and solvent was removed under vacuum and to the residue 2-propanol (40ml) and diisopropyl ether (40ml) were added. After stirring for 30 minutes the solid was filtered, washed twice with diisopropyl ether (20ml each time) and dried in a vacuum oven between 45-50°C for 4 hours. Yield: 10g (80%).

Each method gave clopidogrel hydrogen bromide in polymorph form 2 as determined by DSC, XRPD and TGA (see Figures Two, Five and Eight)

(+)-(S)-Methyl-2-(2-chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate (clopidogrel) hydrogen bromide polymorph form 3

Clopidogrel hydrogen bromide polymorph form 3 was prepared by dissolving clopidogrel hydrogen bromide polymorph form 1 (5g) in 5ml of either methanol or ethanol. Once dissolved at room temperature (~22°C), water (40ml) was added to the solution and stirred. The initial precipitate formed was a sticky solid. This solid

was filtered off and the remaining solution stored in a refrigerator overnight. The white crystals formed in this chilled solution were then filtered using a Buchner filter funnel and dried at 50°C for one hour.

- 5 The crystals were then characterised using DSC, TGA and XRPD (See Figures Three, Six and Nine)

Claims

1. Clopidogrel hydrogen bromide in polymorph form 1.
- 5 2. Clopidogrel hydrogen bromide as claimed in claim 1, having a DSC trace substantially as shown in Figure One, an XRPD spectrum substantially as shown in Figure Four, and/or TGA data substantially as shown in Figure Seven.
3. Clopidogrel hydrogen bromide in polymorph form 2.
- 10 4. Clopidogrel hydrogen bromide as claimed in claim 3, having a DSC trace substantially as shown in Figure Two, an XRPD spectrum substantially as shown in Figure Five, and/or TGA data substantially as shown in Figure Eight.
- 15 5. Clopidogrel hydrogen bromide in polymorph form 3.
6. Clopidogrel hydrogen bromide as claimed in claim 5, having a DSC trace substantially as shown in Figure Three, an XRPD spectrum substantially as shown in Figure Six, and/or TGA data substantially as shown in Figure Nine.
- 20 7. Clopidogrel hydrogen bromide as claimed in any one of claims 1 to 6, wherein the clopidogrel hydrogen bromide is in particulate form.
8. Clopidogrel hydrogen bromide as claimed in any one of claims 1 to 7,
25 wherein the clopidogrel hydrogen bromide is substantially pure.
9. Clopidogrel hydrogen bromide as claimed in any one of claims 1 to 8, for use as a medicament.
- 30 10. Clopidogrel hydrogen bromide as claimed in any one of claims 1 to 9, for inhibiting platelet aggregation.

11. Clopidogrel hydrogen bromide as claimed in any one of claims 1 to 10, for treating, preventing or managing thrombosis, atherothrombosis, an atherothrombotic event, ischaemic stroke, myocardial infarction, non-Q-wave myocardial infarction, atherosclerosis, peripheral arterial disease, or unstable angina.
- 5 12. A process for preparing clopidogrel hydrogen bromide as claimed in any one of claims 1 to 11, comprising the step of precipitating clopidogrel hydrogen bromide from a solution of clopidogrel hydrogen bromide in an organic solvent.
- 10 13. A process as claimed in claim 12, further comprising the step of drying the precipitate.
14. A process as claimed in claim 13, wherein the drying step comprises vacuum drying.
- 15 15. A process as claimed in claim 14, wherein the drying step comprises vacuum drying at a vacuum of down to 50, 40, 35, 30, 25 or 20 mmHg and at a temperature of up to 20, 25, 30, 35, 40, 45, 50, 55 or 60°C.
- 20 16. A process as claimed in any one of claims 12 to 15, wherein the organic solvent is polar, miscible with water, dipolar, and/or aprotic.
17. A process as claimed in any one of claims 12 to 16, wherein the organic solvent comprises a plurality or mixture of solvent compounds.
- 25 18. A process as claimed in any one of claims 12 to 17, wherein the organic solvent is 2-propanol, diisopropyl ether, *t*-butylmethyl ether, dichloromethane, methanol, and/or ethanol.
- 30 19. A pharmaceutical composition, comprising clopidogrel hydrogen bromide as claimed in any one of claims 1 to 11.

20. A pharmaceutical composition as claimed in claim 19, further comprising a pharmaceutically acceptable carrier, excipient or diluent.

21. A pharmaceutical composition as claimed in claim 19 or 20, wherein the
5 composition is for oral administration.

22. A pharmaceutical composition as claimed in any one of claims 19 to 21, wherein the composition is in the form of a tablet or capsule.

10 23. A pharmaceutical composition as claimed in claim 22, wherein the composition is in the form of a tablet and further comprises mannitol, macrogol, microcrystalline cellulose, hydrogenated castor oil, and/or low substituted hydroxypropylcellulose.

15 24. A pharmaceutical composition as claimed in claim 23, wherein the tablet is coated with hypromellose, lactose, triacetin, and/or carnauba wax.

25. A pharmaceutical composition as claimed in any one of claims 19 to 24, wherein the composition is in unit dosage form comprising clopidogrel hydrogen
20 bromide in an amount of from 10mg to 125mg with respect to the free base.

26. A pharmaceutical composition as claimed in any one of claims 19 to 25, for inhibiting platelet aggregation.

25 27. A pharmaceutical composition as claimed in any one of claims 19 to 26, for treating, preventing or managing thrombosis, atherothrombosis, an atherothrombotic event, ischaemic stroke, myocardial infarction, non-Q-wave myocardial infarction, atherosclerosis, peripheral arterial disease, or unstable angina.

30 28. A method of inhibiting platelet aggregation, comprising administering an effective amount of clopidogrel hydrogen bromide as claimed in any one of claims 1 to 11 to a patient in need thereof.

29. A method of treating, preventing or managing a condition selected from thrombosis, atherothrombosis, an atherothrombotic event, ischaemic stroke, myocardial infarction, non-Q-wave myocardial infarction, atherosclerosis, peripheral arterial disease, and unstable angina, comprising administering an effective amount
5 of clopidogrel hydrogen bromide as claimed in any one of claims 1 to 11 to a patient in need thereof.
30. A method as claimed in claim 28 or 29, wherein the patient is a human.
- 10 31. A method as claimed in any one of claims 28 to 30, wherein the amount of clopidogrel hydrogen bromide administered is from 10mg to 125mg with respect to the free base per day.
32. Use of clopidogrel hydrogen bromide as claimed in any one of claims 1 to 11
15 for the preparation of a medicament for inhibiting platelet aggregation.
33. A use as claimed in claim 32, wherein the medicament is for the treatment, prevention or management of thrombosis, atherothrombosis, an atherothrombotic event, ischaemic stroke, myocardial infarction, non-Q-wave myocardial infarction,
20 atherosclerosis, peripheral arterial disease or unstable angina.
34. A process for preparing a polymorphic form of clopidogrel hydrogen sulfate, comprising the step of using clopidogrel hydrogen bromide as claimed in any one of claims 1 to 8.

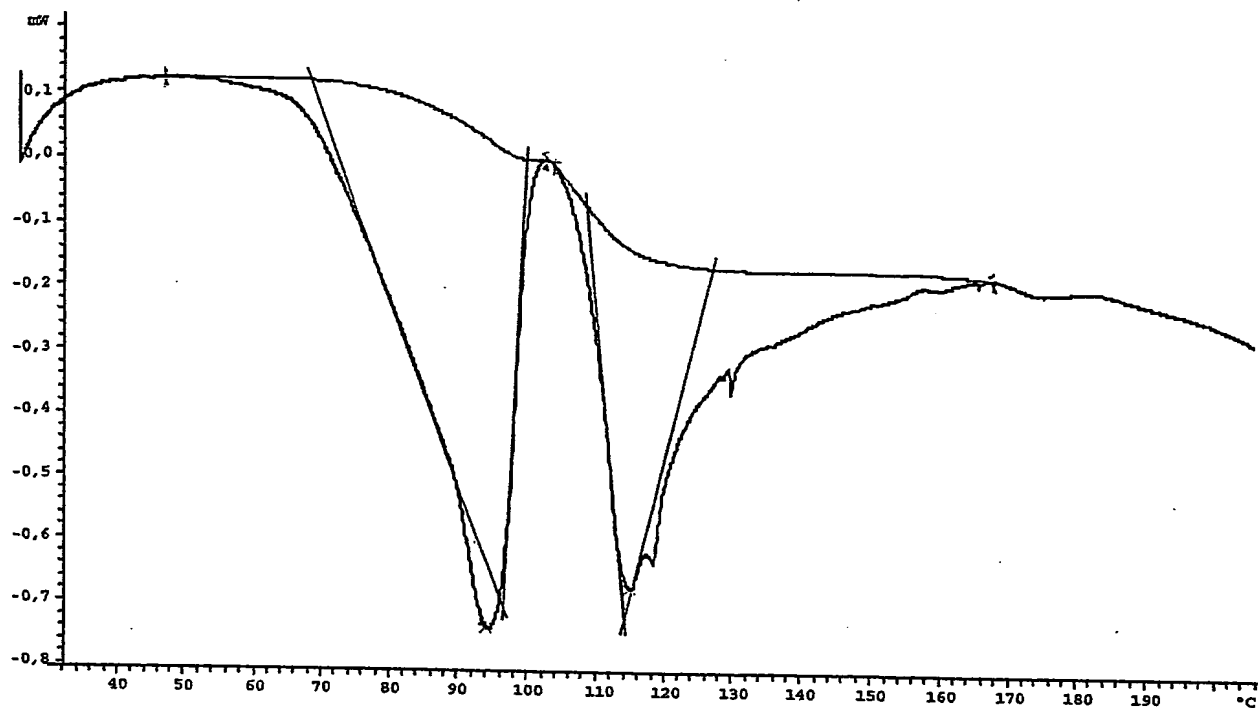


Figure One

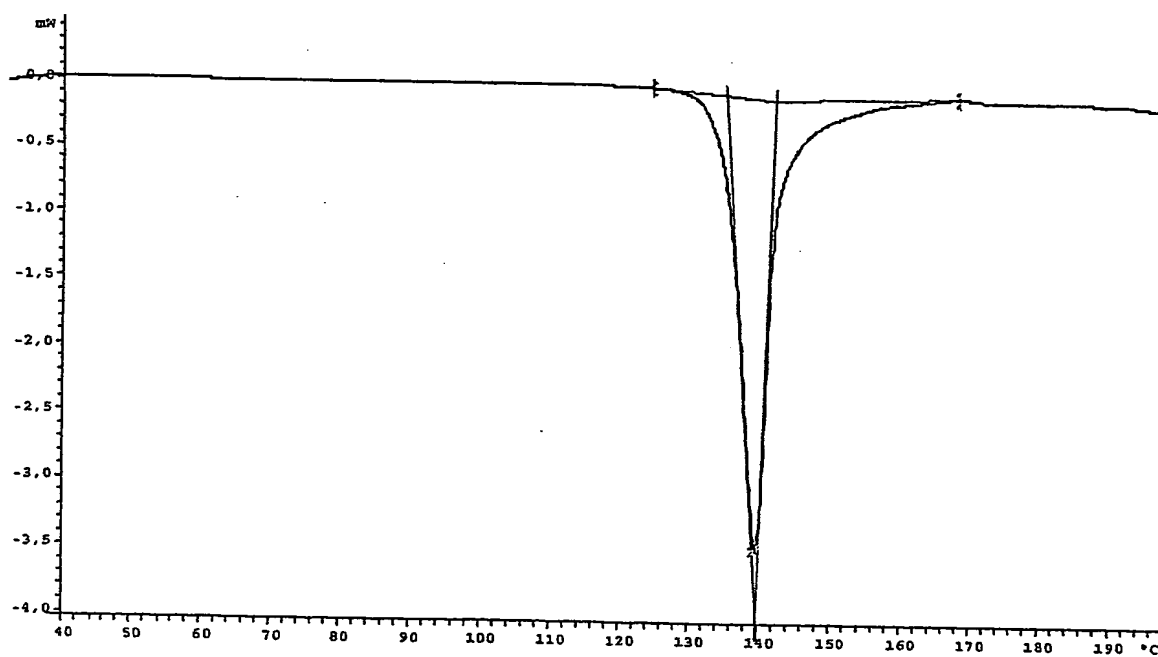


Figure Two

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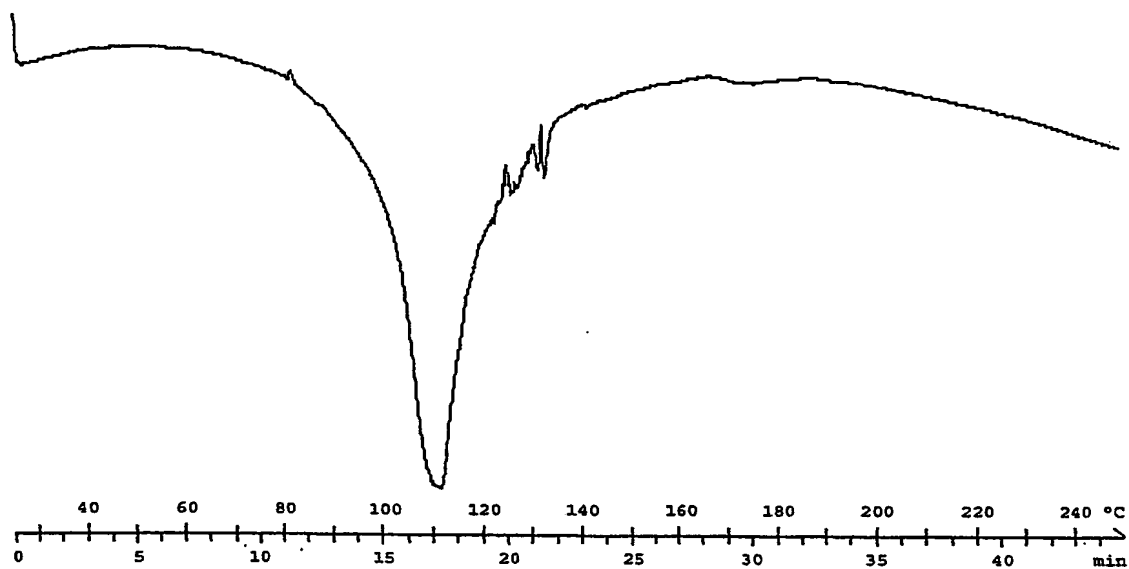


Figure Three

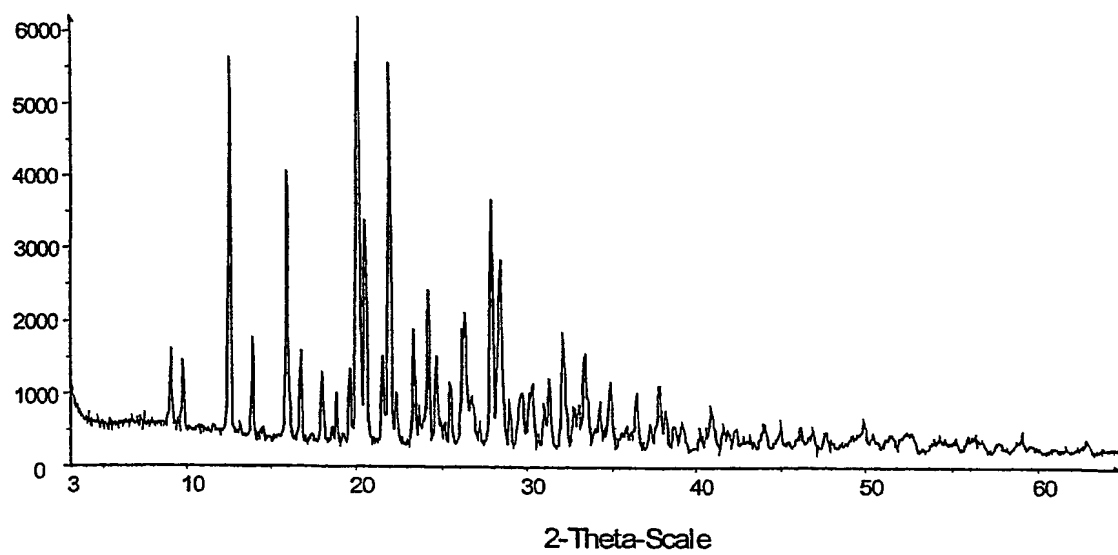


Figure Four

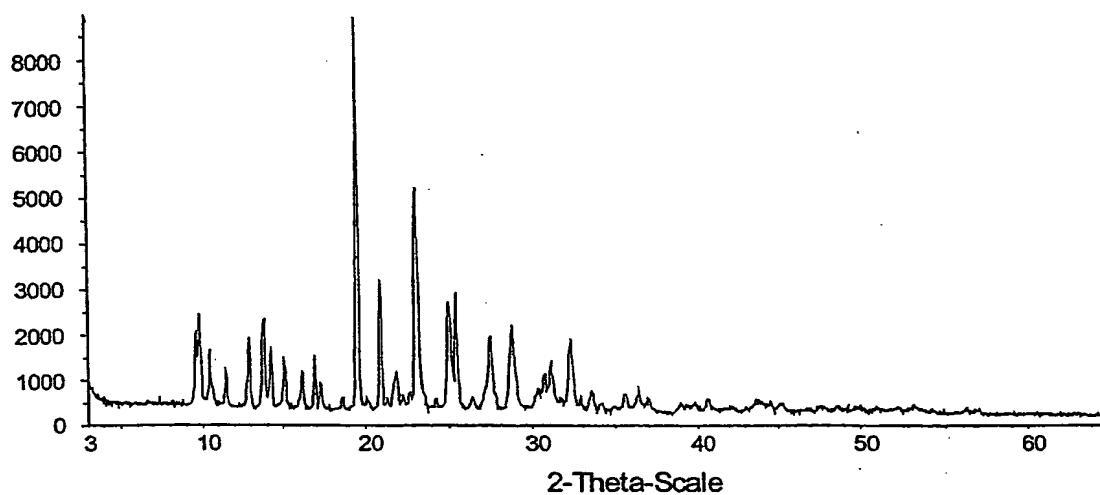


Figure Five

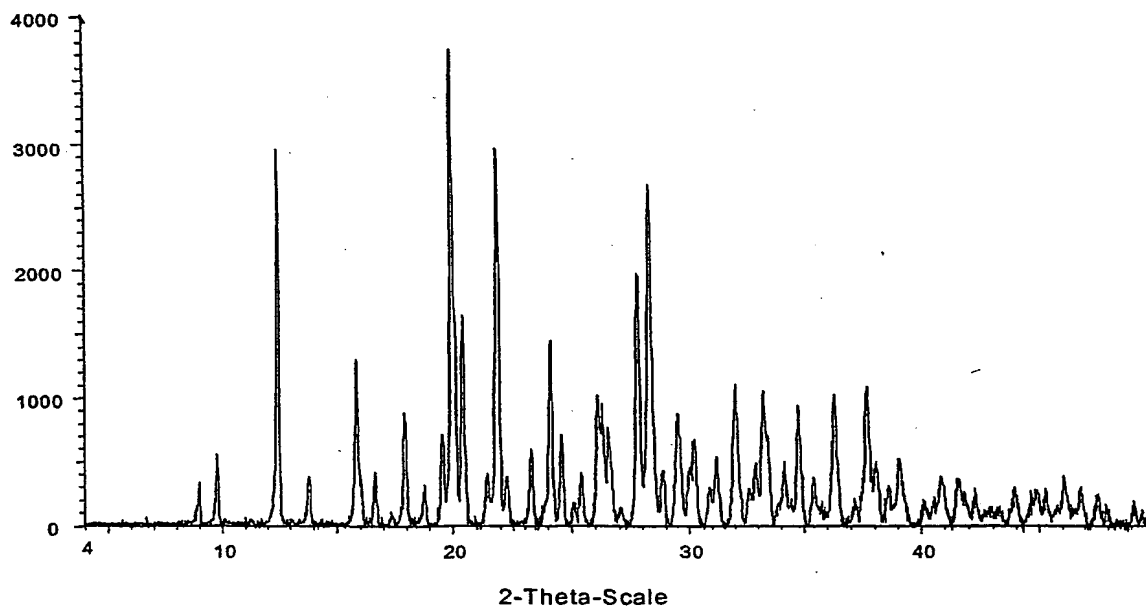


Figure Six

SUBSTITUTE SHEET (RULE 26)

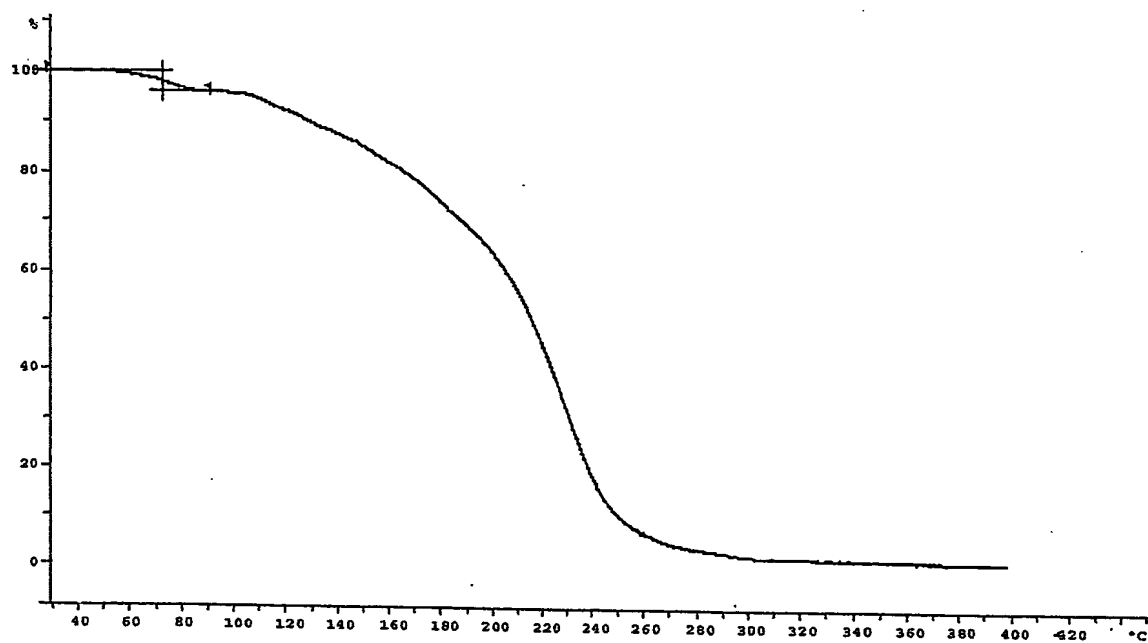


Figure Seven

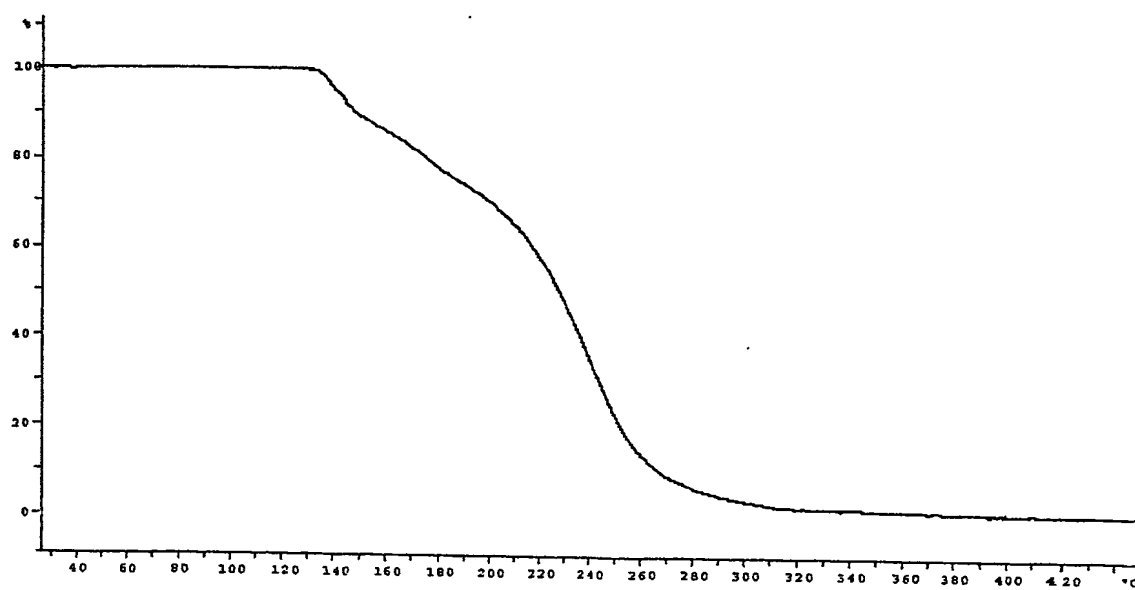


Figure Eight

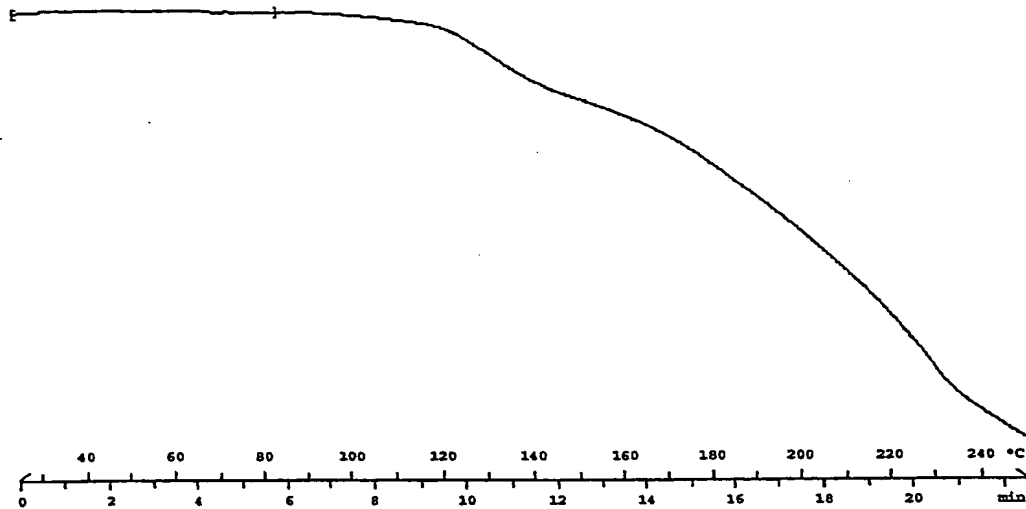


Figure Nine

INTERNATIONAL SEARCH REPORT

 International Application No
 PCT/GB2004/003867

 A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C07D495/04 A61K31/4365 A61P7/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

 Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6 429 210 B1 (BOUSQUET ET. AL.) 6 August 2002 (2002-08-06) cited in the application column 1, line 1 - column 2, line 15; claims; examples	1-34
Y	US 6 180 793 B1 (BAKONYI ET. AL.) 30 January 2001 (2001-01-30) column 1, line 1 - column 2, line 23; claims; examples 11,12	1-34
Y	WO 03/066637 A (EGIS GYOGYSZERGYAR RT.) 14 August 2003 (2003-08-14) page 1 - page 4; claims; examples	1-34
	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *Z* document member of the same patent family

Date of the actual completion of the international search

13 December 2004

Date of mailing of the international search report

17/12/2004

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INTERNATIONAL SEARCH REPORT

Internat. Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MINO R. CAIRA: "Crystalline Polymorphism of Organic Compounds." TOPICS IN CURRENT CHEMISTRY, 1998, XP001156954 HEIDELBERG, DE page 164, line 1 - page 166, line 20 -----	1-34

Form PCT/ISA/210 (continuation of second sheet) (January 2004)

page 2 of 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2004/003867

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 28-31 (part)
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 28-31 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB2004/003867

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